

Atrial high-rate episodes

Bertaglia, Emanuele; Blank, Benjamin; Blomström-Lundqvist, Carina; Brandes, Axel; Cabanelas, Nuno; Dan, G-Andrei; Dichtl, Wolfgang; Goette, Andreas; de Groot, Joris R; Lubinski, Andrzej; Marijon, Eloi; Merkely, Béla; Mont, Lluís; Piorkowski, Christopher; Sarkozy, Andrea; Sulke, Neil; Vardas, Panos; Velchev, Vasil; Wichterle, Dan; Kirchhof, Paulus

DOI:

[10.1093/europace/euz172](https://doi.org/10.1093/europace/euz172)

License:

Creative Commons: Attribution-NonCommercial (CC BY-NC)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Bertaglia, E, Blank, B, Blomström-Lundqvist, C, Brandes, A, Cabanelas, N, Dan, G-A, Dichtl, W, Goette, A, de Groot, JR, Lubinski, A, Marijon, E, Merkely, B, Mont, L, Piorkowski, C, Sarkozy, A, Sulke, N, Vardas, P, Velchev, V, Wichterle, D & Kirchhof, P 2019, 'Atrial high-rate episodes: prevalence, stroke risk, implications for management, and clinical gaps in evidence', *Europace*, vol. 21, no. 10, pp. 1459-1467. <https://doi.org/10.1093/europace/euz172>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

© The Author(s) 2019. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>)

Emanuele Bertaglia, Benjamin Blank, Carina Blomström-Lundqvist, Axel Brandes, Nuno Cabanelas, G -Andrei Dan, Wolfgang Dichtl, Andreas Goette, Joris R de Groot, Andrzej Lubinski, Eloi Marijon, Béla Merkely, Lluís Mont, Christopher Piorkowski, Andrea Sarkozy, Neil Sulke, Panos Vardas, Vasil Velchev, Dan Wichterle, Paulus Kirchhof, Atrial high-rate episodes: prevalence, stroke risk, implications for management, and clinical gaps in evidence, EP Europace, euz172. <https://doi.org/10.1093/europace/euz172>

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Atrial high-rate episodes: prevalence, stroke risk, implications for management, and clinical gaps in evidence

Emanuele Bertaglia¹, Benjamin Blank², Carina Blomström-Lundqvist³, Axel Brandes^{4,5}, Nuno Cabanelas⁶, G.-Andrei Dan⁷, Wolfgang Dichtl⁸, Andreas Goette^{2,9}, Joris R. de Groot¹⁰, Andrzej Lubinski¹¹, Eloi Marijon¹², Béla Merkely¹³, Lluís Mont¹⁴, Christopher Piorkowski¹⁵, Andrea Sarkozy¹⁶, Neil Sulke¹⁷, Panos Vardas¹⁸, Vasil Velchev¹⁹, Dan Wichterle²⁰, and Paulus Kirchhof^{2,21*}

¹Department of Cardiac, Vascular and Thoracic Sciences, Azienda Ospedaliera, Padua, Italy; ²Atrial Fibrillation NETwork (AFNET), Muenster, Germany; ³Department of Medical Science, Uppsala University, Uppsala, Sweden; ⁴Department of Clinical Research, University of Southern Denmark, Odense, Denmark; ⁵Department of Cardiology, Odense University Hospital, Odense, Denmark; ⁶Arrhythmias Unit of Cardiology Department, Hospital Prof. Dr. Fernando Fonseca, Amadora-Sintra, Portugal; ⁷Colentina University Hospital, Medicine Clinical Institute "Carol Davila", Bucharest, Romania; ⁸University Hospital of Internal Medicine III, Medical University Innsbruck, Innsbruck, Austria; ⁹St. Vincenz Hospital Paderborn, Cardiology and Intensive Care Medicine, Paderborn, Germany; ¹⁰Department of Cardiology, Heart Center, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands; ¹¹Department of Interventional Cardiology and Arrhythmias, Medical University of Lodz, Lodz, Poland; ¹²Cardiac Electrophysiology Section, European Georges Pompidou Hospital, Paris, France; ¹³Heart and Vascular Center, Semmelweis University Budapest, Budapest, Hungary; ¹⁴Cardiovascular Clinical Institute, Hospital Clinic, Universitat de Barcelona, Catalonia, Spain; ¹⁵Herzzentrum Dresden GmbH, Universitätsklinikum, Dresden, Germany; ¹⁶Universitair Ziekenhuis Antwerpen, Edegem, Belgium; ¹⁷Eastbourne District General Hospital, Eastbourne, UK; ¹⁸Heart Sector, Hygeia Group Hospitals, Athens, Greece; ¹⁹Cardiology Clinic, St. Anna University Hospital, Medical University Sofia, Sofia, Bulgaria; ²⁰Institute for Clinical and Experimental Medicine, Prague, Czech Republic; and ²¹Institute of Cardiovascular Sciences, University of Birmingham, UHB and Sandwell & West Birmingham Hospitals NHS Trusts, IBR 126a, Wolfson Drive, Birmingham B15 2TT, UK

Received 18 March 2019; editorial decision 26 May 2019; accepted 15 July 2019

Self-terminating atrial arrhythmias are commonly detected on continuous rhythm monitoring, e.g. by pacemakers or defibrillators. It is unclear whether the presence of these arrhythmias has therapeutic consequences. We sought to summarize evidence on the prevalence of atrial high-rate episodes (AHREs) and their impact on risk of stroke. We performed a comprehensive, tabulated review of published literature on the prevalence of AHRE. In patients with AHRE, but without atrial fibrillation (AF), we reviewed the stroke risk and the potential risk/benefit of oral anticoagulation. Atrial high-rate episodes are found in 10–30% of AF-free patients. Presence of AHRE slightly increases stroke risk (0.8% to 1%/year) compared with patients without AHRE. Atrial high-rate episode of longer duration (e.g. those >24h) could be associated with a higher stroke risk. Oral anticoagulation has the potential to reduce stroke risk in patients with AHRE but is associated with a rate of major bleeding of 2%/year. Oral anticoagulation is not effective in patients with heart failure or survivors of a stroke without AF. It remains unclear whether anticoagulation is effective and safe in patients with AHRE. Atrial high-rate episodes are common and confer a slight increase in stroke risk. There is true equipoise on the best way to reduce stroke risk in patients with AHRE. Two ongoing trials (NOAH-AFNET 6 and ARTESiA) will provide much-needed information on the effectiveness and safety of oral anticoagulation using non-vitamin K antagonist oral anticoagulants in patients with AHRE.

Keywords

Atrial fibrillation • Atrial high-rate episodes • Pacemaker • Stroke • Anticoagulation • Continuous monitoring

* Corresponding author. Tel: +44 121 414 7042. E-mail address: p.kirchhof@bham.ac.uk

© The Author(s) 2019. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Introduction

The increased use of cardiac implantable electronic devices (CIED) and their technical ability to monitor atrial rhythm and to identify even very short episodes of atrial arrhythmias has transformed our understanding of these events in the last 10–15 years. Having an atrial lead implanted, CIED can detect episodes of atrial tachyarrhythmias including atrial tachycardia, atrial flutter, and atrial fibrillation (AF). These episodes, which are commonly asymptomatic and only detected through long-term continuous rhythm monitoring by a CIED, are described as atrial high-rate episodes (AHREs) and must be distinguished from asymptomatic episodes of paroxysmal AF, which are diagnosed through surface electrocardiographic methods^{1–4}. Some AHRE do not represent true atrial tachyarrhythmias, but reflect artefacts.⁵ In addition, the biological relevance of very rare AHRE, which will usually not be detected by occasional electrocardiograms (ECGs), remains unknown.

Here, we provide a comprehensive review of the prevalence of AHRE, their impact on stroke risk and current implications for management. While others have used the term 'sub-clinical AF', we use AHRE in this review, partially reflecting the diagnostic uncertainty, the high prevalence of AHRE compared with ECG-documented AF, and their spurious association with overt AF and with AF-related outcomes.

Prevalence of atrial high-rate episodes in patients undergoing continuous atrial rhythm monitoring

Atrial high-rate episodes have been reported in several large observational studies with different design, cohort size, patient characteristics, duration of follow-up, detection algorithms, and definition of AHRE in terms of atrial rate and duration (Table 1). Most of these studies included unselected patients with common indications for pacemaker or implantable cardioverter-defibrillator,^{6–15} while others analysed populations with heart failure or risk factors for stroke.^{16–23} Most studies used an atrial rate limit of >175 or >180 to define an AHRE,^{6,11,12,16–18,20} while a few others used atrial rates that were even higher.^{7,19,21} Atrial high-rate episodes were reported in 10% in the SAFE registry and in 70% in the analysis of data from the Veterans Administration Health Care System (Table 1). Importantly, studies including patients with the clinical diagnosis AF, which *per se* have a higher frequency of atrial arrhythmias, found AHRE in 40–70%.^{1,6–9,11,13,16,20,21,23} Studies excluding patients with known AF have found AHRE in 10–30% of patients % (Figure 1).^{10,12,14,17–19,22}

The minimal duration of AHRE varied from three premature atrial complexes—much below the threshold for a sustained atrial arrhythmia in the view of most experts—in the RATE Registry to up to 14 min in the pooled analysis from the HOME Care and EVEREST trials,^{15,20} with the majority of studies using an episode duration longer than 5–6 min to define AHRE.^{7,9,10,12,14,17–19,22,23} This duration seems to be a 'diagnostic sweet spot' that allows most algorithms detecting AHRE to distinguish artefacts from true atrial arrhythmias. This duration has not been selected based on biological relevance (e.g. association with stroke risk). There is a clear relation between the detection

of AHRE and the duration of monitoring, e.g. illustrated in the ASSERT trial that found AHRE in 10% of patients within the first 3 months after enrolment, and in an additional 24.5% during the subsequent mean follow-up of 2.5 years.^{19,24}

The high AHRE detection rates spurred discussion whether these rates are generalizable, e.g. reflecting that these patients all had arrhythmias requiring a CIED which may also create a substrate for AHRE^{3,25} and potentially a proarrhythmic effect in the first few weeks after implantation of a new atrial lead.^{12,26} Several studies using subcutaneous implantable loop recorders (ILRs) have largely refuted these considerations, at least in patients with stroke risk factors. These devices detect QRS complexes and determine AHRE using similar algorithms based on ventricular rate and its regularity.^{27,28} Implantation of an ILR in stroke survivors, often after usual work-up for AF including Holter monitoring, found AHRE in 4–34% of patients, depending on monitoring duration and patient characteristics (Table 2).^{29–40} Implantable loop recorders also detect AHREs in 21–58% of patients with cardiovascular conditions, but without an indication for rhythm monitoring (Table 3),^{41–45} i.e. with comparable rates as in pacemaker populations. Thus, these data suggest that AHRE are common in patients with cardiovascular conditions undergoing long-term continuous monitoring of atrial rhythm.

Patients with atrial fibrillation, including those with paroxysmal atrial fibrillation, are at sufficient risk for cardioembolic stroke to benefit from oral anticoagulation for stroke prevention

Atrial fibrillation in rheumatic heart disease was recognized as a factor that predisposes to systemic embolism in 1951.⁴⁶ Left atrial emboli causing ischaemic stroke were described a decade later.⁴⁷ In the Framingham Heart Study, AF was associated with a five-fold long-term increased risk of stroke.^{48,49} Prospective randomized studies from the late 1980s reported a dramatic and highly significant reduction in stroke in patients with AF treated with warfarin. The randomized AFASAK,⁵⁰ SPAF,⁵¹ and BAATAF⁵² studies were among the first to demonstrate that dose-adjusted warfarin prevented strokes effectively in patients with AF, confirmed in a later meta-analysis.⁵³

Until recently, the risk of thromboembolism has been considered to be independent of AF type.^{54–57} Previous systematic reviews of risk factors for stroke in AF patients have not identified AF type as an important prognostic risk factor for thromboembolism.^{58–60} Atrial fibrillation stroke risk prediction models have, in general, not included AF type^{61–64} perhaps because of absence of AF pattern information in hospitalization/discharge databases that were used for their derivation and validation. This consensus of risk equivalence between AF patterns is reflected by Class I and IIa recommendations in current European⁵⁵ and North American⁵⁴ guidelines.

Vanassche *et al.*⁶⁵ pooled the data on aspirin-treated patients ($n = 6573$) from the ACTIVE-A and AVERROES trials. Atrial fibrillation pattern was a strong independent predictor of risk for

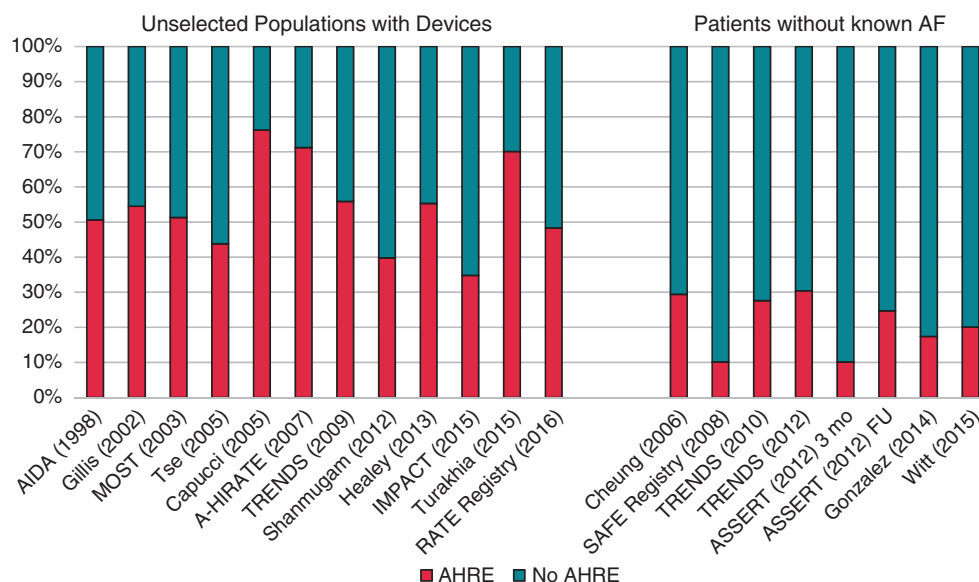


Figure 1 Percentage of AHRE in patients with (left panel) and without (right panel) known AF. AF, atrial fibrillation; AHRE, atrial high-rate episode.

Table 1 Incidence of CIED-detected AHRE

Study	Number of patients	Mean age (years)	% male	Duration of follow-up	Definition of AHRE	Patients with AHRE
AIDA (1998)	617	70 ± 11	62%	28 days	≥1 min (the AIDA algorithm)	179/354 (50.6%)
Gillis <i>et al.</i> (2002)	231	70 ± 12	52%	718 ± 383 days	Atrial rate >180 b.p.m. for ≥1 min; sustained AF >250 b.p.m. for >1 min	126/231 (54.5%) (AF)
MOST (2003)	312	74	45%	Median 27 months	Atrial rate >220 b.p.m. for >5 min	160/312 (51.3%)
Tse <i>et al.</i> (2005)	226	72 ± 10 in patients with detected AF; 70 ± 10 in patients without detected AF	39%	84 ± 16 months	Any AT detected by the device	99/226 (43.8%)
Capucci <i>et al.</i> (2005)	725	71 ± 11	50%	Median 22 months (16–30)	AF >5 min; AF >1 day	76.2%; 56.3%
Cheung <i>et al.</i> (2006)	262	74 ± 12	54%	596 ± 344 days	AHRE ≥5 min	77/262 (29%)
A-HIRATE (2007)	427	75 ± 9	56%	24 months	Atrial rate >180 b.p.m. for ≥1 min	53.8% in patients without previous AT; 88.6% in patients with previous AT
SAFE registry (2008)	1482	74 ± 12	56%	Median 349 ± 147 days	Atrial rate ≥180 b.p.m. for ≥5 min	150/1482 (10.1%)
TRENDS (2009)	2486	71 ± 11	66.4%	Median 1.4 years (0.1–3.3)	Atrial rate >175 b.p.m. for ≥20 s	1389/2486 (55.9%)

Continued

Table 1 Continued

Study	Number of patients	Mean age (years)	% male	Duration of follow-up	Definition of AHRE	Patients with AHRE
TRENDS (2010)	163	74.0 ± 9.1 in patients with AHRE; 72.8 ± 9.9 in patients without AHRE	71.1% in patients with AHRE; 62.7% in patients without AHRE	1.1 ± 0.7 years	Atrial rate >175 b.p.m. for ≥5 min	45/163 (27.6%)
TRENDS (2012)	1368	70.2 ± 11.8	66.2%	1.1 ± 0.7 years	Atrial rate >175 b.p.m. for ≥5 min	416/1368 (30.4%)
ASSERT (2012)	2580	77 ± 7 in patients with AHRE; 76 ± 7 in patients without AHRE	56.3% in patients with AHRE; 58.6% in patients without AHRE	Mean 2.5 years	Atrial rate ≥190 b.p.m. for >6 min; all episodes confirmed by manual expert review of electrograms	261/2580 (10.1%) within 3 months after device implantation; 633/2566 (24.6%) during further follow-up
Shanmugam et al. (2012)	560	66 ± 10	77.4%	Median 370 days (253–390)	Atrial rate >180 b.p.m. for ≥14 min	223/560 (39.8%); 126/382 without history of AF, 97/178 with history of AF
Healey et al. (2013)	445	74.3 ± 13.7 in patients with AHRE; 71.7 ± 14.4 in patients without AHRE	58% in patients with AHRE, 59% in patients without AHRE	51.5 ± 39.7 months	Any PM detected AF (manufacturer-specific nominal settings for AF detection)	246/445 (55.3%)
Gonzalez et al. (2014)	224	74 ± 12	53%	6 months after PM implantation	Any device-detected AHRE ≥5 min	39/224 (17.4%)
IMPACT (2015)	2718	Median 64.4	73.7%	Median 701 days	Atrial rate ≥200 b.p.m. for ≥36 of 48 atrial beats	945/2718 (34.8%)
Witt et al. (2015)	394	Median 67 years (59–74)	74%	Median 4.2 years (2.5–6.6)	Manufacturer-specific nominal settings for AF detection; AHREs >6 min	79/394 (20.0%)
Turakhia et al. (2015)	187	68 ± 8.4	99.5%	120 days	AF ≥6 min	70.1% (26.2% ≥6 min of AF; 24.6% ≥1 h of AF; 19.3% ≥5.5 h of AF)
RATE Registry (2016)	5379	73.6 ± 11.8 in patients with PM; 64.5 ± 12.6 in patients with ICD	54.1% with PM; 72.4% with ICD	Median 22.9 months	≥3 premature atrial complexes	145/300 (48%) with PM and 155/300 (52%) with ICD of the representative random sample studied

AF, atrial fibrillation; AHRE, atrial high-rate episode; AT, atrial tachycardia; CIED, cardiac implantable electronic devices; ICD, implantable cardioverter-defibrillator; PM, pacemaker.

embolic event (ischaemic or unspecified stroke or systemic embolism). The ACTIVE-W trial found a trend towards higher stroke (and systemic embolism) rates in persistent/permanent compared with paroxysmal AF in non-anticoagulated patients but not in warfarin-

treated patients.⁵⁷ Similarly, the data from Friberg et al.⁶⁶ did not show a significant overall difference in stroke rates according to AF pattern, but found an increase in ischaemic stroke in the subgroup of non-anticoagulated patients with permanent compared with

Table 2 Incidence of ILR-detected subclinical AF in patients with cryptogenic stroke or transient ischaemic attack

Study	Number of patients included	Mean age (years)	% male	Mean CHA ₂ DS ₂ -VASc score	Duration of follow-up	Definition of AHRE	Patients with AHRE	Time to first AHRE episode
Dion et al. (2010)	24	49 ± 13.6	62.5%	NR	Mean 14.5 months	Ventricular rate >165 b.p.m. for >32 complexes	1/24 (4.2%) with AF <30 s	NR
Cotter et al. (2013)	51	51.5 ± 13.9	54.9%	Median 3 (2–4)	Mean 229 ± 112 days in patients without AHRE	AF >2 min	13/51 (25.5%)	Median 48 days (0–154)
Ritter et al. (2013)	60	Median 63 (48.5–72.0)	56.7%	Median 4 (3–5) without AHRE; median 4 (3–5) with AHRE	Median 397 days (337–504) without AHRE; median 312 days (242–397) with AHRE	AF >2 min	10/60 (16.7%)	Median 64 days (1–556)
Etgen et al. (2013)	22	60.0 without AF; 65.8 with AF	43.8% without AF; 66.7% with AF	NR	12 months	AF ≥6 min	6/22 (27.3%)	Mean 152.8
Rojo-Martinez et al. (2013)	101	67	46.5%	NR	281 ± 212 days	AF >2 min	34/101 (33.7%)	Median 102 days (26–240)
SURPRISE (2014)	85	54.0 without AF; 66.9 with AF	58.0% without AF; 44.4% with AF	Median 3 without AHRE; median 4 with AHRE	569 ± 310 days	AF >2 min	18/85 (20.7%)	109 ± 48 days
CRYSTAL AF (2014)	441 (208 ICM)	61.5 ± 11.3	63.5%	NR	12 months	AF >2 min	8.9% at 6 months; 12.4% at 12 months	Median 41 days (14–84)
CRYSTAL AF (2016)	48 (24 ICM)?	61.6 ± 11.4	?	NR	36 months	AF >2 min	30%	?
Poli et al. (2016)	74	66.4 ± 12.5	47%	Median 5 (4–6)	12 months	AF >2 min	21/74 (28.4%) at 6 months; 25/74 (33.8%) at 12 months	105 ± 135 days
Israel et al. (2017)	123	65.0 ± 9.4	60.2%	4.5 ± 1.3	12.7 ± 5.5 months	AF ≥2 min	29/123 (23.6%)	Average 3.6 months
Reinke et al. (2018)	105	64.4 ± 12.6	56.2%	Median 4 (3–6)	?	AF >2 min	19/105 (18%)	Median 217 days (72.5–338)
Pedersen et al. (2018)	105	Median 65.4 (27.1–80.8)	45.7%	Median 4 (2–7)	Median 381 days (371–390)	AF ≥2 min	7/105 (6.7%)	Median 21 days (5–146)

?, not reported; AF, atrial fibrillation; AHRE, atrial high-rate episode; ILR, implantable loop recorders; ICM, intracardiac monitor; NR, not recorded.

Table 3 Incidence of ILR-detected subclinical AF in patients at high risk of stroke

Study	Number of patients	Mean age (years)	% male	Duration of follow-up	Definition of AHRE	Patients with AHRE	Time to first AHRE
ASSERT-II (2017)	273	73.9 ± 6.2	65.6%	16.3 ± 3.8 months	AF including AFL and AT ≥5 min	90/256 (35.2%)	5.1 ± 5.5 months
REVEAL AF (2017)	446	71.5 ± 9.9	52.3%	22.5 ± 7.7 months	AF ≥6 min	29.3% at 18 months; 6.2%, 20.4%, 27.1%, 33.6%, and 40.0% at 1, 6, 12, 24, and 30 months	Median 123 days (41–330)
PREDATE AF (2017)	245	74.3 ± 7.7	58.8%	18 months; mean follow-up 451 ± 185 days	AF ≥6 min	55/245 (22.4%)	141.3 ± 139.5 days
Philippsen et al. (2017)	82	71 ± 4.0	63%	Median 588 days (453–712)	AF ≥2 min	17/82 (20.7%); 14/82 (17%) AF ≥6 min	Median 91 days (41–251)
Romanov et al. (2018)	50	57.8 ± 8.3	88%	≥24 months	AF ≥2 min	29/50 (58%) at 24 months; 16%, 40%, 50%, and 54% at 3, 6, 12, and 18 months	Median 4.8 months

AF, atrial fibrillation; AFL, atrial flutter; AHRE, atrial high-rate episode; ILR, implantable loop recorders.

paroxysmal AF. Recent trials in anticoagulated AF patients reported lower stroke rates in paroxysmal vs. non-paroxysmal AF patients (SPORTIF,⁶⁷ ARISTOTLE,⁶⁸ and ENGAGE-AF⁶⁹). A meta-analysis combining data from >95 000 patients⁷⁰ appears to confirm that stroke risk may be slightly lower in patients with paroxysmal AF compared with those with chronic AF.

Patients at high stroke risk without atrial fibrillation do not benefit from oral anticoagulation

Oral anticoagulation using either vitamin K antagonists such as warfarin or non-vitamin K antagonist oral anticoagulants (NOACs) has been tested in several conditions predisposing for stroke other than AF usually without evidence for effectiveness.

Anticoagulants in survivors of a stroke without atrial fibrillation

Conducted almost 20 years ago, the WARSS trial could not detect a clinical benefit of warfarin [target international normalized ratio (INR) 1.4–2.8] over 325 mg aspirin per day after a non-cardioembolic ischaemic stroke in patients without AF within 2 years.⁷¹ In patients with a recent embolic stroke of undetermined source, the NAVIGATE ESUS trial has been stopped in 2017 due to no efficacy improvement of 15 mg rivaroxaban over 100 mg aspirin daily, with an increased risk of bleeding in patients randomized to rivaroxaban.⁷² A similar trial with dabigatran, the RE-SPECT ESUS study, similarly reported no reduction in stroke rates in patients randomized to dabigatran, with increased clinically relevant major bleedings compared to aspirin.⁷³

Anticoagulants in patients with other neurological disorders

The CADISS trial tested warfarin vs. aspirin in patients with symptomatic carotid and vertebral artery dissection.⁷⁴ No difference was detected between oral anticoagulation or single antiplatelet treatment. The WASID trial compared warfarin (target INR 2.0–3.0) with high-dose aspirin (1300 mg per day) in patients with transient ischaemic attack or stroke caused by a 50–99% stenosis of a major intracranial artery.⁷⁵ This study was stopped prematurely after 569 patients because of a significantly higher bleeding rate without any benefit in the warfarin arm.

Anticoagulation in patients with heart failure, but without atrial fibrillation

The WARCEF trial showed no difference between long-term warfarin and aspirin treatment in 2305 patients with a left ventricular ejection fraction below 35% and sinus rhythm.⁷⁶ The primary composite endpoint (ischaemic stroke, intracerebral haemorrhage, and death from any cause) comprised 7.47 events per 100 patient-years in the warfarin group and 7.93 in the aspirin group. COMMANDER-HF confirmed that rivaroxaban, albeit at a lower dose than the dose approved for stroke prevention in AF, was not effective in prevention of strokes compared with no anticoagulation in a similar heart failure population.⁷⁷

Risk of bleeding in patients treated with oral anticoagulants

The benefit of oral anticoagulation in patients with AF can so far only be achieved by exposing patients to an increased bleeding risk.^{72,78} Non-vitamin K antagonist oral anticoagulant treatment is associated with a markedly lower rate of intracranial haemorrhage and lower mortality than Vitamin K antagonist therapy,⁷⁹ but the bleeding rate on NOACs is still important (ca. 2% per year of exposure), both in clinical trials⁷⁹ and in patients exposed to NOACs under routine care conditions.^{80–83} In summary, the bleeding rates associated with different NOACs in real-world patients vary from 1.9% to 4.3% per year of treatment. Absolute rates depend on patient characteristics such as age. Notably, these findings on the rates of major bleeding with NOACs are comparable with the major bleeding rates reported in the pivotal randomized clinical trials.

The average atrial high-rate episodes burden is only a few hours per year, and the majority of patients with atrial high-rate episodes never receive a clinical diagnosis of atrial fibrillation

Current anticoagulation guidelines in non-valvular AF are supported by studies in patients with ECG-documented AF episodes, whether symptomatic or not.^{84,85} Clinical diagnosis of AF in patients with AHRE was evaluated more than 10 years ago in the Ancillary MOST substudy,⁷ performed in 312 patients included in the MOST study.⁸⁶ The population was heterogeneous, and patients with previously documented AF were not excluded. Selected patients had a pacemaker implanted due to sinus node dysfunction but were in sinus rhythm at randomization, and the analysis was retrospective and observational. During a median follow-up of 27 months, AHREs were detected in 160 patients (51.3%). Twenty of these patients had AF history documented before AHRE detection. Of the remaining 140 patients without previous AF, 36 (25.7%) had AF documented during follow-up. Similar or lower rates of AF detection were found in the ASSERT and ASSERT II studies.

Hence, although AHRE renders detection of ECG-documented AF more likely, the majority (>75%) of patients with AHRE never develop ECG-documented AF in the subsequent years, probably due to the infrequent and short nature of AHRE episodes in most patients.

Stroke risk in atrial high-rate episode patients is lower than in patients with paroxysmal atrial fibrillation

There is a growing body of evidence on the stroke risk in patients with AHREs. In the ASSERT study, the annual thromboembolic event rate was 1.7% in patients with AHRE within 3 months after inclusion,

compared with 0.7% in patients who did not show AHRE within 3 months after inclusion. These numbers are comparable to a recent systematic review where patients with AHRE had an annual stroke rate of 1.9%, compared with 0.9% in patients without AHRE.⁸⁸ Recently, a subanalysis from ASSERT focused on the longest AHRE episode found that only AHRE >24 h was associated with an increased risk of stroke compared with absence of AHRE.⁸⁷ This is much lower than the stroke risk that can be expected in patients with a similar stroke risk profile and ECG documented AF. Interestingly, strokes occur equally during periods with and without AHRE in patients with AHRE suffering a stroke.⁸⁹ Furthermore, the current licences of NOACs do not explicitly allow their use in patients with AHRE. Thus, also in view of the bleeding risk associated with anticoagulation, we do not know whether to use oral anticoagulation in patients with AHRE.

Summary: equipoise for oral anticoagulation in patients with atrial high-rate episode

Most modern pacemakers, defibrillators, and cardiac resynchronization devices provide automated algorithms alerting to AHRE. A growing body of clinical data supports the hypothesis that AHREs are associated with an elevated risk of developing further clinical AF and stroke, but the stroke risk is substantially lower than in patients with ECG-detected AF, most likely due to the very rare and short nature of AHRE episodes.⁹⁰ In view of the small but substantial risk of major bleeding in patients treated with oral anticoagulants, including NOACs, there is currently no justification for oral anticoagulation in patients with AHRE. Two ongoing studies, NOAH-AFNET 6⁹¹ and ARTESiA,⁹² will address the key question of whether patients with AHRE benefit from oral anticoagulation. ARTESiA (Apixaban for the Reduction of Thrombo-Embolic in Patients With Device-Detected Sub-Clinical AF) aims to enroll 4000 high-risk (CHA₂DS₂-VASc score ≥3) participants with permanent pacemakers, defibrillators, or resynchronization device, and at least one AHRE episode of 6 min to 24 h duration (atrial rate >175/min if an atrial lead is present).⁹² Patients will be randomized to receive apixaban or aspirin. The primary efficacy outcome is ischaemic stroke or systemic embolism; the primary safety outcome is major bleeds. The NOAH-AFNET 6 study (NOAC in patients with AHRE) trial is recruiting ca 3000 patients aged >65 years with one additional CHA₂DS₂-VASc factor and AHRE documented by CIED (≥170 b.p.m. atrial rate and ≥6 min duration).⁹¹ These patients will be randomized to edoxaban or aspirin/placebo, depending on the indications for antiplatelet therapy. The primary outcome parameter of NOAH-AFNET 6 is a composite of stroke, systemic embolism, or cardiovascular death.

The results of these two trials have the potential to inform future guidance on the management of patients with atrial arrhythmias detected by implantable devices. Until these trials have reported, treatment with oral anticoagulants should be limited to rare individual decisions in patients with AHRE, but without ECG-diagnosed AF, to avoid the substantial bleeding risk on anticoagulation.

Funding

This work was largely written by voluntary contributions of time from the authors. It was partially supported by British Heart Foundation (FS/13/43/30324 to P.K.; PG/17/30/32961 to P.K.), German Centre for Cardiovascular Research supported by the German Ministry of Education and Research (DZHK, via a grant to AFNET) and by Leducq Foundation.

Conflict of interest: J.R.d.G. receives consultant or speaker fees from Atricure, Daiichi Sankyo, Bayer and Novartis. He received research funding through institution from Abbot, Boston Scientific, Medtronic, Atricure and Owner RhythmCare. A.G. receives lecture fees from Sanofi, Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, Medtronic, Omeicos, and Astra-Zeneca. P.K. receives research support from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation and has received honoraria from several such companies. P.K. is listed as inventor on two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). P.V. receives personal fees from Menarini International, Dean Medicus, Servier, European Society of Cardiology, Bayer and Hygeia Hospitals group. All other authors declared no conflict of interest.

References

- Defaye P, Dournaux F, Mouton E. Prevalence of supraventricular arrhythmias from the automated analysis of data stored in the DDD pacemakers of 617 patients: the AIDA study. The AIDA Multicenter Study Group. Automatic Interpretation for Diagnosis Assistance. *Pacing Clin Electrophysiol* 1998;**21**:250–5.
- Todd D, Hernandez-Madrid A, Proclemer A, Bongiorni MG, Estner H, Blomstrom-Lundqvist C et al. How are arrhythmias detected by implanted cardiac devices managed in Europe? Results of the European Heart Rhythm Association Survey. *Europace* 2015;**17**:1449–53.
- Freedman B, Boriani G, Glotzer TV, Healey JS, Kirchhof P, Potpara TS. Management of atrial high-rate episodes detected by cardiac implanted electronic devices. *Nat Rev Cardiol* 2017;**14**:701–14.
- Camm AJ, Simantirakis E, Goette A, Lip GY, Vardas P, Calvert M et al. Atrial high-rate episodes and stroke prevention. *Europace* 2017;**19**:169–79.
- Kaufman ES, Israel CW, Nair GM, Armaganjian L, Divakaramenon S, Mairesse GH et al. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: an analysis from ASSERT. *Heart Rhythm* 2012;**9**:1241–6.
- Gillis AM, Morck M. Atrial fibrillation after DDDR pacemaker implantation. *J Cardiovasc Electrophysiol* 2002;**13**:542–7.
- Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinichak R et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MoDe Selection Trial (MOST). *Circulation* 2003;**107**:1614–9.
- Tse HF, Lau CP. Prevalence and clinical implications of atrial fibrillation episodes detected by pacemaker in patients with sick sinus syndrome. *Heart* 2005;**91**:362–4.
- Capucci A, Santini M, Padeletti L, Gulizia M, Botto G, Boriani G et al. Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. *J Am Coll Cardiol* 2005;**46**:1913–20.
- Cheung JW, Keating RJ, Stein KM, Markowitz SM, Iwai S, Shah BK et al. Newly detected atrial fibrillation following dual chamber pacemaker implantation. *J Cardiovasc Electrophysiol* 2006;**17**:1323–8.
- Orlov MV, Ghali JK, Araghi-Niknam M, Sherfese L, Sahr D, Hettrick DA et al. Asymptomatic atrial fibrillation in pacemaker recipients: incidence, progression, and determinants based on the atrial high rate trial. *Pacing Clin Electrophysiol* 2007;**30**:404–11.
- Mittal S, Stein K, Gilliam FR 3rd, Kraus SM, Meyer TE, Christman SA. Frequency, duration, and predictors of newly-diagnosed atrial fibrillation following dual-chamber pacemaker implantation in patients without a previous history of atrial fibrillation. *Am J Cardiol* 2008;**102**:450–3.
- Healey JS, Martin JL, Duncan A, Connolly SJ, Ha AH, Morillo CA et al. Pacemaker-detected atrial fibrillation in patients with pacemakers: prevalence, predictors, and current use of oral anticoagulation. *Can J Cardiol* 2013;**29**:224–8.

14. Gonzalez M, Keating RJ, Markowitz SM, Liu CF, Thomas G, Ip JE et al. Newly detected atrial high rate episodes predict long-term mortality outcomes in patients with permanent pacemakers. *Heart Rhythm* 2014;**11**:2214–21.
15. Swiryn S, Orlov MV, Benditt DG, DiMarco JP, Lloyd-Jones DM, Karst E et al. Clinical implications of brief device-detected atrial tachyarrhythmias in a cardiac rhythm management device population: results from the registry of atrial tachycardia and atrial fibrillation episodes. *Circulation* 2016;**134**:1130–40.
16. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol* 2009;**2**:474–80.
17. Ziegler PD, Glotzer TV, Daoud EG, Ezekowitz MD, Singer DE, Koehler JL et al. Incidence of newly detected atrial arrhythmias via implantable devices in patients with a prior history of stroke. *Stroke* 2009;**40**:E186–7.
18. Ziegler PD, Glotzer TV, Daoud EG, Singer DE, Ezekowitz MD, Hoyt RH et al. Detection of previously undiagnosed atrial fibrillation in patients with stroke risk factors and usefulness of continuous monitoring in primary stroke prevention. *Am J Cardiol* 2012;**110**:1309–14.
19. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–9.
20. Shanmugam N, Boerdlein A, Proff J, Ong P, Valencia O, Maier SK et al. Detection of atrial high-rate events by continuous home monitoring: clinical significance in the heart failure-cardiac resynchronization therapy population. *Europace* 2012;**14**:230–7.
21. Martin DT, Bersohn MM, Waldo AL, Wathen MS, Chouairi WK, Lip GY et al. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. *Eur Heart J* 2015;**36**:1660–8.
22. Witt CT, Kronborg MB, Nohr EA, Mortensen PT, Gerdes C, Nielsen JC. Early detection of atrial high rate episodes predicts atrial fibrillation and thromboembolic events in patients with cardiac resynchronization therapy. *Heart Rhythm* 2015;**12**:2368–75.
23. Turakhia MP, Ziegler PD, Schmitt SK, Chang YC, Fan J, Than CT et al. Atrial fibrillation burden and short-term risk of stroke case-crossover analysis of continuously recorded heart. *Circ Arrhythm Electrophysiol* 2015;**8**:1040–7.
24. Charitos EI, Stierle U, Ziegler PD, Baldewig M, Robinson DR, Sievers HH et al. A comprehensive evaluation of rhythm monitoring strategies for the detection of atrial fibrillation recurrence: insights from 647 continuously monitored patients and implications for monitoring after therapeutic interventions. *Circulation* 2012;**126**:806–14.
25. Monfredi O, Boyett MR. Sick sinus syndrome and atrial fibrillation in older persons—a view from the sinoatrial nodal myocyte. *J Mol Cell Cardiol* 2015;**83**:88–100.
26. Wiesel J, Subclinical SM. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:1351; author reply 1352–1353.
27. Hindricks G, Pokushalov E, Urban L, Taborsky M, Kuck KH, Lebedev D et al. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: results of the XPECT trial. *Circ Arrhythm Electrophysiol* 2010;**3**:141–7.
28. Nölker G, Mayer J, Boldt LH, Seidl K, Vand V, Massa T et al. Performance of an implantable cardiac monitor to detect atrial fibrillation: results of the DETECT AF study. *J Cardiovasc Electrophysiol* 2016;**27**:1403–10.
29. Dion F, Saudeau D, Bonnaud I, Friocourt P, Bonneau A, Poret P et al. Unexpected low prevalence of atrial fibrillation in cryptogenic ischemic stroke: a prospective study. *J Interv Card Electrophysiol* 2010;**28**:101–7.
30. Cotter PE, Martin PJ, Ring L, Warburton EA, Belham M, Pugh PJ. Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. *Neurology* 2013;**80**:1546–50.
31. Ritter MA, Kochhauser S, Duning T, Reinke F, Pott C, Dechering DG et al. Occult atrial fibrillation in cryptogenic stroke: detection by 7-day electrocardiogram versus implantable cardiac monitors. *Stroke* 2013;**44**:1449–52.
32. Etgen T, Hochreiter M, Mundel M, Freudenberger T. Insertable cardiac event recorder in detection of atrial fibrillation after cryptogenic stroke: an audit report. *Stroke* 2013;**44**:2007–9.
33. Rojo-Martinez E, Sandin-Fuentes M, Calleja-Sanz AI, Cortijo-Garcia E, Garcia-Bermejo P, Ruiz-Pinero M et al. [High performance of an implantable Holter monitor in the detection of concealed paroxysmal atrial fibrillation in patients with cryptogenic stroke and a suspected embolic mechanism]. *Rev Neurol* 2013;**57**:251–7.
34. Christensen LM, Krieger DW, Hojberg S, Pedersen OD, Karlens FM, Jacobsen MD et al. Paroxysmal atrial fibrillation occurs often in cryptogenic ischaemic stroke. Final results from the SURPRISE study. *Eur J Neurol* 2014;**21**:884–9.
35. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478–86.
36. Brachmann J, Morillo CA, Sanna T, Di Lazzaro V, Diener HC, Bernstein RA et al. Uncovering atrial fibrillation beyond short-term monitoring in cryptogenic stroke patients: three-year results from the cryptogenic stroke and underlying atrial fibrillation trial. *Circ Arrhythm Electrophysiol* 2016;**9**:e003333.
37. Poli S, Diedler J, Hartig F, Gotz N, Bauer A, Sachse T et al. Insertable cardiac monitors after cryptogenic stroke—a risk factor based approach to enhance the detection rate for paroxysmal atrial fibrillation. *Eur J Neurol* 2016;**23**:375–81.
38. Israel C, Kitsiou A, Kalyani M, Deelawar S, Ejangue LE, Rogalewski A et al. Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders. *Thromb Haemost* 2017;**117**:1962–9.
39. Reinke F, Bettin M, Ross LS, Kochhauser S, Kleffner I, Ritter M et al. Refinement of detecting atrial fibrillation in stroke patients: results from the TRACK-AF Study. *Eur J Neurol* 2018;**25**:631–6.
40. Pedersen KB, Madsen C, Sandgaard NCF, Diederichsen ACP, Bak S, Brandes A. Subclinical atrial fibrillation in patients with recent transient ischemic attack. *J Cardiovasc Electrophysiol* 2018;**29**:707–14.
41. Healey JS, Alings M, Ha A, Leong-Sit P, Birnie DH, de Graaf JJ et al. Subclinical atrial fibrillation in older patients. *Circulation* 2017;**136**:1276–83.
42. Reiffel JA, Verma A, Kowey PR, Halperin JL, Gersh BJ, Wachter R et al. Incidence of previously undiagnosed atrial fibrillation using insertable cardiac monitors in a high-risk population: the REVEAL AF study. *JAMA Cardiol* 2017;**2**:1120–7.
43. Nasir JM, Pomeroy W, Marler A, Hann M, Baykaner T, Jones R et al. Predicting determinants of atrial fibrillation or flutter for therapy elucidation in patients at risk for thromboembolic events (PREDATE AF) study. *Heart Rhythm* 2017;**14**:955–61.
44. Philippsen TJ, Christensen LS, Hansen MG, Dahl JS, Brandes A. Detection of subclinical atrial fibrillation in high-risk patients using an insertable cardiac monitor. *JACC Clin Electrophysiol* 2017;**3**:1557–64.
45. Romanov A, Martinek M, Purerfellner H, Chen S, De Melis M, Grazhdankin I et al. Incidence of atrial fibrillation detected by continuous rhythm monitoring after acute myocardial infarction in patients with preserved left ventricular ejection fraction: results of the ARREST study. *Europace* 2018;**20**:263–70.
46. Daley R, Mattingly TW, Holt CL, Bland EF, White PD. Systemic arterial embolism in rheumatic heart disease. *Am Heart J* 1951;**42**:566–81.
47. Askey JM, Bernstein S. The management of rheumatic heart disease in relation to systematic arterial embolism. *Prog Cardiovasc Dis* 1960;**3**:220–32.
48. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978;**28**:973–7.
49. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;**22**:983–8.
50. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1989;**1**:175–9.
51. Preliminary report of the stroke prevention in atrial fibrillation study. *N Engl J Med* 1990;**322**:863–8.
52. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;**323**:1505–11.
53. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;**131**:492–501.
54. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;**64**:e1–76.
55. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;**12**:1360–420.
56. Hart RG, Pearce LA, Rothbart RM, McNulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000;**35**:183–7.
57. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S et al. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W substudy. *J Am Coll Cardiol* 2007;**50**:2156–61.
58. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;**69**:546–54.
59. Hughes M, Lip GY. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost* 2008;**99**:295–304.

60. Pisters R, Lane DA, Marin F, Camm AJ, Lip GY. Stroke and thromboembolism in atrial fibrillation. *Circ J* 2012;**76**:2289–304.
61. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–70.
62. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Euro Heart Survey* 2010;**137**:263–72.
63. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc* 2013;**2**: e000250.
64. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;**290**:1049–56.
65. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M et al. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J* 2015;**36**: 281–7a.
66. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J* 2010;**31**: 967–75.
67. Lip GY, Frison L, Grind M. Stroke event rates in anticoagulated patients with paroxysmal atrial fibrillation. *J Intern Med* 2008;**264**:50–61.
68. Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D et al. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. *Eur Heart J* 2013;**34**:2464–71.
69. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–104.
70. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J* 2016;**37**: 1591–602.
71. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;**345**:1444–51.
72. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;**378**:2191–201.
73. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019;**380**:1906–17.
74. Markus HS, Hayter E, Levi C, Feldman A, Venables G, Norris J. Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial. *Lancet Neurol* 2015;**14**:361–7.
75. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005;**352**:1305–16.
76. Homma S, Thompson JL, Pulicino PM, Levin B, Freudenberger RS, Teerlink JR et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012;**366**:1859–69.
77. Zannad F, Anker SD, Byra WM, Cleland JGF, Fu M, Gheorghide M et al. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. *N Engl J Med* 2018;**379**:1332–42.
78. Group ES, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. *Lancet Neurol* 2007;**6**:115–24.
79. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–62.
80. Graham DJ, Reichman ME, Werneck M, Zhang R, Southworth MR, Levenson M et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation* 2015;**131**:157–64.
81. Kirchhof P, Radaideh G, Kim YH, Lanas F, Haas S, Amarencio P et al. Global prospective safety analysis of rivaroxaban. *J Am Coll Cardiol* 2018;**72**:141–53.
82. Staerk L, Fosbol EL, Lip GYH, Lamberts M, Bonde AN, Torp-Pedersen C et al. Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study. *Eur Heart J* 2017;**38**:907–15.
83. Halvorsen S, Ghanima W, Fridtveit I, Hoxmark C, Falck P, Solli O et al. A nationwide registry study to compare bleeding rates in patients with atrial fibrillation being prescribed oral anticoagulants. *Eur Heart J Cardiovasc Pharmacother* 2017;**3**:28–36.
84. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
85. Kirchhof P, Curtis AB, Skanes AC, Gillis AM, Samuel Wann L, John Camm A. Atrial fibrillation guidelines across the Atlantic: a comparison of the current recommendations of the European Society of Cardiology/European Heart Rhythm Association/European Association of Cardiothoracic Surgeons, the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society, and the Canadian Cardiovascular Society. *Eur Heart J* 2013;**34**:1471–4.
86. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med* 2002;**346**:1854–62.
87. Van Gelder IC, Healey JS, Crijns H, Wang J, Hohnloser SH, Gold MR et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J* 2017;**38**:1339–44.
88. Mahajan R, Perera T, Elliott AD, Twomey DJ, Kumar S, Munwar DA et al. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. *Eur Heart J* 2018;**39**:1407–15.
89. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014;**129**:2094–9.
90. Gorenek B, Bax J, Boriani G, Chen SA, Dagres N, Glotzer TV et al. Device-detected subclinical atrial tachyarrhythmias: definition, implications and management—an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). *Europace* 2017;**19**:1556–78.
91. Kirchhof P, Blank BF, Calvert M, Camm AJ, Chlouverakis G, Diener HC et al. Probing oral anticoagulation in patients with atrial high rate episodes: rationale and design of the Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes (NOAH-AFNET 6) trial. *Am Heart J* 2017;**190**:12–18.
92. Lopes RD, Alings M, Connolly SJ, Beresh H, Granger CB, Mazuecos JB et al. Rationale and design of the Apixaban for the Reduction of Thrombo-Embolicism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial. *Am Heart J* 2017;**189**:137–45.